HIGH PRODUCTION VOLUME (HPV)

CHEMICALS CHALLENGE PROGRAM

TEST PLAN

For

HEXANEDIOIC ACID, DI-C7-C9 BRANCHED AND LINEAR ALKYL ESTER (97 ADIPATE)

CAS NO. 68515-75-3

Prepared by:

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EXECUTIVE SUMMARY

Solutia Inc. voluntarily submits the following screening information data and Test Plan covering the chemical, Hexanedioic acid, Di C7-C9 branched and linear alkyl ester or 97 Adipate (CAS No. 68515-75-3), for review under the Environmental Protection Agency's High Production Volume (HPV) Chemicals Challenge Program.

A substantial amount of data exists to evaluate the potential hazards associated with 97 Adipate. Use of key studies available from data already developed provide adequate support to characterize each Endpoint in the HPV Chemicals Challenge Program without the need for additional unnecessary testing.

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TEST PLAN FOR 97 ADIPATE

I. INTRODUCTION AND IDENTIFICATION OF CHEMICAL

Under EPA's High Production Volume (HPV) Chemicals Challenge Program, Solutia Inc. has committed to voluntarily compile basic screening data on Hexanedioic acid, Di-C7-C9 Branched and Linear Alkyl Ester, also known as 97 Adipate. The data included in this Test Plan involve physicochemical properties, environmental fate, and human and environmental effects of 97 Adipate, as defined by the Organization for Economic Cooperation and Development (OECD). The information provided comes from existing data developed on behalf of Solutia Inc. or found in the published scientific literature or from estimation modeling and fulfills Solutia's obligation to the HPV Challenge Program.

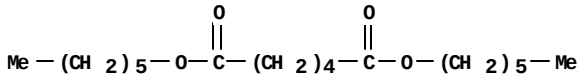
A. Structure and Nomenclature

Following is a characterization of 97 Adipate and associated nomenclature.

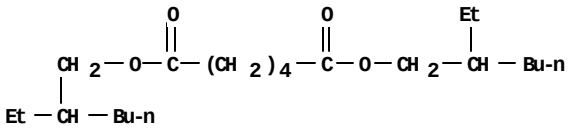
97 Adipate is classified as a UVCB chemical (i.e. a Chemical Substance of Unknown or Variable Composition, Complex Reaction Products and Biological Materials) on the TSCA Chemical Substance Inventory (US EPA, 1985). As such, it does not have a defined structure to depict here. Following is the appropriate nomenclature to reference 97 Adipate:

Hexanedioic acid, di-C7-9-branched and linear alkyl esters
CAS No. 68515-75-3
Synonyms: 97 Adipate, Dialkyl Adipate, Santicizer 97, Santicizer 97A

Two additional adipic acid esters, both closely related structurally to 97 Adipate, have been used to provide surrogate data for the Mutagenicity – Chromosomal Aberration Endpoint, as described in Section IV.D.3.0 of this Dossier. Following are their structures:



Di(n-Hexyl) Adipate
CAS No. 110-33-8
Synonyms: DHA; Santicizer 367; XA-2562 Plasticizer



Dioctyl Adipate
CAS No. 103-23-1
Synonyms: DOA; Di(2-ethylhexyl)adipate; DEHA

B. Manufacturing and Use

97 Adipate is a plasticizer formed by reacting adipic acid with a mixture of lightly branched heptyl and nonyl alcohols. It is specifically designed to give PVC film, sheet and coatings excellent low-temperature flexibility. End products which might contain this plasticizer include coated fabrics or sheeting for rainwear, film for luggage and accessories, and coated industrial fabrics exposed to refrigeration. It is used to plasticize rubber formulations. It imparts good low temperature flexibility to nitrile rubber without reducing its heat aging performance.

It is also used in food packaging, especially for foods which need to be refrigerated or frozen. 97 Adipate complies with US Department of Agriculture regulations for use as an acceptable component of packaging materials in contact with meat or poultry food products prepared under Federal inspection. It is also used in certain indirect food contact applications regulated under sections 175, 176, 177 and 178 of Title 21, Code of Federal Regulations.

97 Adipate is manufactured at one plant in Canada and is imported by Solutia Inc. into the United States. The manufacturing process is a closed process and follows typical Good Manufacturing Practices.

II. TEST PLAN RATIONALE

The data obtained and included to support this Test Plan have come from either 1) internal studies conducted by/or for Solutia Inc. (or its predecessor Monsanto Co.), 2) have been extracted from the scientific literature either as primary references or as found in well-accepted, peer-reviewed reference books, 3) were estimated using environmental models accepted by the US EPA (1999b), or 4) were associated with structurally similar adipate esters and thus found useful to provide a “read across” assessment of a single (Chromosomal Aberration) HPV Endpoint.

The basic screening data derived for this initial assessment include information on physicochemical properties, environmental fate, and human and environmental effects associated with 97 Adipate. The data used to support this program include those endpoints identified by the US EPA (1998); key studies for 97 Adipate have been identified for each data Endpoint and are summarized in Robust Summary form and included in Section VI, which accompanies this Dossier. Robust summaries of relevant mutagenicity studies conducted with DHA and DOA, two Adipic acid ester surrogates used in this assessment are also included in Section VI.

All studies were reviewed and assessed for reliability according to standards specified by Klimisch et al (1997), as recommended by US EPA (1999a). The following criteria were used for codification:

1. Reliable without Restrictions – Includes studies which comply with US EPA and/or OECD-accepted testing guidelines, which were conducted using Good Laboratory Practices (GLPs) and for which test parameters are complete and well documented.

2. Reliable with Restrictions – Includes studies which were conducted according to national/international testing guidance and are well documented. May include studies conducted prior to establishment of testing standards or GLPs but meet the test parameters and data documentation of subsequent guidance; also includes studies with test parameters which are well documented and scientifically valid but vary slightly from current testing guidance. Also included were physical-chemical property data obtained from reference handbooks as well as environmental endpoint values obtained from an accepted method of estimation (i.e. EPIWIN).

3. Not Reliable – Includes studies in which there are interferences in either the study design or results that provide scientific uncertainty or where documentation is insufficient.

4. Not Assignable – Not used in this Dossier.

Those studies receiving a Klimisch rating of 1 or 2 are considered adequate to support data assessment needs in this Dossier.

III. TEST PLAN SUMMARY AND CONCLUSIONS

Conclusion: All HPV Endpoints have been satisfied with a combination of data from studies that were either well documented, used OECD guideline methods and conducted in accord with GLPs, or were estimated from acceptable estimation

modeling programs. In a single case (Chromosomal Aberration), use of reliable, well conducted studies from two structurally similar surrogate chemicals supports a conclusion that no additional information is needed on 97 Adipate; hence, no further testing is planned, as summarized in Table 1.

In summary:

Physical-chemical property values (Boiling Point, Vapor Pressure, Partition Coefficient and Water Solubility) were obtained from Solutia-derived studies to characterize each of these properties. No Melting Point data is available, or considered applicable, as 97 Adipate is a liquid at room temperature. A rating of "2-Reliable with restrictions" has been assigned to these studies.

Environmental Fate information dealing with Water Stability (Hydrolysis) and Transport (Fugacity) were estimated using a computer estimation-modeling program (EPIWIN, 2002) recommended by EPA (US EPA, 1999b), as no data could be found for either Endpoint. Thus, they have been designated as "2-Reliable with restrictions". Well-conducted and documented studies characterizing Photodegradation and Biodegradation fulfilled each of these Endpoint requirements and have been designated "2-Reliable with restrictions" and "1-Reliable without restriction", respectively.

Each of the three **Ecotoxicity** data (Acute Fish, Acute Invertebrate and Acute Algae Toxicity) Endpoint requirements was met with a respective aquatic toxicity study considered "2-Reliable with restrictions".

Mammalian Toxicity Endpoints for Acute Toxicity and Repeated Dose Toxicity were met with completion of an acute oral rat study and a 13-Week rat toxicity study. As both of these well-documented studies were conducted prior to codification of OECD/GLP guidance, they have been coded "2-Reliable with restrictions"; no effects on the gonads were observed in the 13-Week Subchronic study. Although no study is available addressing Reproductive Toxicity, a Developmental Toxicity study, considered as "1-Reliable without restriction", has been conducted with 97 Adipate. Therefore, according to EPA Guidance (US EPA, 1998a), use of the combination Subchronic study and the Developmental Toxicity study (meeting OECD 414 guidance) will fulfill the HPV Reproductive Toxicity Endpoint. The Ames testing Endpoint is fulfilled with a study classified as "1-Reliable without restriction". No Chromosomal Aberration study has been conducted with 97 Adipate. However, in vivo studies which evaluate the potential to cause chromosomal damage, all of which are considered "1-Reliable without restriction" are available for two adipate esters closely related structurally to 97 Adipate. These studies are deemed adequate for "Read across" evaluation to support this HPV Endpoint for 97 Adipate.

Following is a tabular summary of the Test Plan developed for 97 Adipate.

Table 1. Test Plan Summary for 97Adipate

	Info. Avail.?	OECD?	GLP?	Other Study?	Estimat. Method?	Accept-Able ?	Testing Recomm.?
PHYSICAL CHEMICAL							
Melting Point	N	-	-	-	N	Y	N
Boiling Point	Y	N	N	Y	N	Y	N
Vapor Pressure	Y	N	N	Y	N	Y	N
Partition Coefficient	Y	N	N	Y	N	Y	N
Water Solubility	Y	N	N	Y	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	N	Y	Y	N	Y	N
Stability in Water	Y	-	-	N	Y	Y	N
Biodegradation	Y	Y	N	N	N	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	N	Y	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	N	Y	Y	N	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	N	Y	Y	N	Y	N
Toxicity to Aquatic Plants	Y	N	Y	Y	N	Y	N
MAMMALIAN TOXICITY							
Acute Toxicity	Y	N	N	N	N	Y	N
Repeated Dose Toxicity	Y	N	N	N	N	Y	N
Genetic Toxicity – Mutation (Ames)	Y	Y	Y	N	N	Y	N
Genetic Toxicity – Chromosomal Aberrations	N	-	-	S	N	Y	N
Developmental Toxicity	Y	Y	Y	N	N	Y	N
Reproductive Toxicity	N	-	-	-	N	C	N

Y= Yes; N = No; C = Completed thru combo of Developmental Toxicity and Subchronic Toxicity Endpoints; S = Completed using Surrogate study data; - = Not applicable

IV. DATA SET SUMMARY AND EVALUATION

The key studies used in this assessment to fulfill the HPV requirements have been placed in an Endpoint-specific matrix and further discussed below. Robust Summaries for each study referenced in these tables can be found in Section VI of this Dossier.

A. Chemical/Physical Properties

Table 2. Selected Physical-Chemical Properties of 97 Adipate

Chemical	Boiling Pt. (^{o}C.)	Melting Pt.(^{o} C.)	Vapor Pressure (hPa @ 224 ^{o}C)	Water Solubility (mg/L)	Log Kow
97-Adipate CAS No. 68515-75-3	224	n.a.	13	< 0.048	6.48

n.a. = not applicable; substance is a liquid at room temperature.

All relevant HPV Endpoints for Physical-Chemical Properties have been completed with reliable information taken from well documented studies sufficient to characterize each Endpoint and have been used broadly for that purpose. These studies have been designated as "2-Reliable with restrictions". As 97 Adipate is a liquid at room temperature, there is no melting point value available, nor is one needed.

In summary, 97 Adipate is a liquid with low vapor pressure. It possesses exceedingly low solubility in water and a high Partition coefficient. A calculated bioconcentration factor of >1000 is reflective of its potential to accumulate in biological tissue, unless degradation or metabolism occurs, which is likely, based on comparison to DOA, a structurally similar chemical. The octanol/water Partition coefficient of 97 Adipate and DOA were determined in the same study (Solutia study no. ES-80-SS-41); DOA had a partition coefficient (7.14) and an estimated bioconcentration factor (>2700) even higher than 97 Adipate. Detailed follow up studies with DOA (Felder et al, 1986), confirmed rapid and extensive metabolism and biodegradation occurring in aquatic systems, such that the actual measured bioconcentration factor of DOA (after a 28-d test in bluegills) was 27. A similar rapid and extensive metabolism/biodegradation in the environment would be expected with 97 Adipate.

Conclusion – Adequate studies are available to provide needed information in the physical-chemical properties associated with 97 Adipate. Therefore, no additional data development is needed for these HPV Endpoints.

B. Environmental Fate and Biodegradation

Information obtained from estimation modeling and laboratory testing with 97 Adipate describe the environmental fate and biodegradation characteristics of this chemical, and are highlighted in Table 3. Each of the studies represented in Table 3 are summarized in detail in the Robust Summary section of this Dossier.

Table 3. Environmental Fate and Biodegradation Properties of 97-Adipate

Chemical	Biodegradation Rate (24 hr)	Stability in Water	Fugacity	Photodegradation Rate
97-Adipate CAS No. 68515-75-3	67-88 %	3.21 yrs	Air- 0.3 Water- 3.6 Soil - 27.3 Sed.- 68.8	0 % (14 days)

A well-conducted and documented biodegradation study, which evaluated 97 Adipate for Ready (SCAS Test) and Ultimate Biodegradation (C02 Evolution Test), supports the Biodegradation HPV Endpoint and has been classified as "1-Reliable without restriction". 97 Adipate was also evaluated for Photodegradation potential. Follow up testing was conducted to resolve a question of microbial contamination, which allowed reasoned scientific conclusions to be drawn from this study, which is classified as "2-Reliable with restrictions", to support this Endpoint. Both Fugacity and Stability in Water Endpoints were completed using the EPIWIN (2002) estimation model, as recommended by US EPA (1999b); thus, they have been classified as "2-Reliable with restrictions". The water stability is best estimated for 97 Adipate since it is impossible to conduct the recommended OECD #111 Test with this material. That Test Guideline requires that the test substance be soluble at a level of 20 mM. The calculated water solubility of 97 Adipate is < 48 ppb or 0.13 uMol (based on Mol. Wt. of 356.55 g/Mol), thus rendering the test impractical and any such results analytically meaningless.

In summary, 97 Adipate will partition almost exclusively into the soil/sediment environmental compartment where it is readily biodegradable. While essentially no Photodegradation or hydrolysis can be expected, 97 Adipate is degraded rapidly through bacterial action with no apparent acclimation or induction period apparently being needed to initiate or carry out the process. Limited amounts of 97 Adipate are expected in the aqueous compartment, as it possesses exceedingly low water solubility where it will be degraded via bacterial action.

Conclusion – Adequate studies are available to provide needed information for each of the HPV Environmental Properties associated with 97 Adipate. No additional testing is recommended.

C. Aquatic Toxicity

Each of the three acute aquatic toxicity studies used to support the HPV Aquatic Toxicity Endpoints were well-conducted studies that followed US EPA testing guidance; the methods used were similar to, and subsequently codified, into OECD testing guidance. All studies were conducted in accord with GLPs. Due to the exceedingly low water solubility (< 48 ppb) of 97 Adipate, each study was conducted above this level. In all cases, no interference was observed (i.e. no toxicity observed at the nominal dosage levels used nearest the solubility limit) between test article and test species. Thus, this limitation did not detract from the conclusions reached for an assessment of each study, i.e., 97 Adipate produces no acute toxicity up to levels of aqueous solubility. Based on the limited solubility factor, the results as reported in these studies, and as summarized in Table 4, should be considered in excess of the actual value (i.e. NOEL = 0.048 mg/L) and thus were considered "2-Reliable with restrictions". These studies are, however, fully adequate to fulfill the HPV data requirements for its Endpoint.

Table 4. Aquatic toxicity parameters for 97-Adipate

Chemical	Fish LC 50 (mg/L)	Invertebrate LC50 (mg/L)	Algae EC50 (mg/L)
97-Adipate CAS No. 68515-75-3	>1,000 (96-h trout)	1.9 (48-h daphnia)	2.5 (96-h)

In summary, 97 Adipate produces no overt acute toxicity in any of the three aquatic species tested up to the level of water solubility (< 48 ppb).

Conclusion – Adequate studies are available on fish, aquatic invertebrates and algae in order to assess the acute aquatic toxic hazards associated with 97 Adipate. Therefore, no additional data development is needed for these HPV endpoints.

D. Mammalian Toxicity

Table 5. Summary of Mammalian Toxicity of 97-Adipate

Chemical Name/ CAS no.	Acute Toxicity		Repeat Dose Toxicity.	Developmental Toxicity
	OLD50 (Rat)	DLD50 (Rabbit)	90-Day (Rat oral)	Rat (oral)
97-Adipate CAS No. 68515-75-3	>15,800 mg/kg	> 7,940 mg/kg	NOEL = 2.5 % in diet	NOEL (terata) = 7,000 mg/kg NOEL (embryo/feto) = 4,000 mg/kg NOEL (maternal) = 4,000 mg/kg

1.0 Acute Toxicity

Results of acute toxicity studies by both the oral and dermal routes of exposure have been conducted and Robust Summaries prepared in the Dossier section below. Both studies were conducted prior to inception of OECD and GLP guidelines, but used methodology consistent with OECD testing for the Acute Toxicity Endpoint. The acute oral toxicity study, which is a Minimum Lethal Dose assay, is considered the key study for this HPV Endpoint and fulfills the data needs in this area. The Dermal Minimum Lethal Dose study has been included as Supplemental information. Both studies are considered as "2-Reliable with restrictions".

97 Adipate is considered to be practically non-toxic after acute oral or dermal exposure.

Conclusion – An available acute toxicity study is sufficient to assess the acute hazards associated with 97 Adipate. Therefore, no additional data development is needed for this HPV Endpoint.

2.0 Repeated Dose Toxicity

97 Adipate has been tested in rats by the dietary route for 90 consecutive days (Table 4). A Robust Summary of this study has been included in the appropriate section of this Dossier. As it was conducted consistent with, but prior to, codification of OECD Test guidance (# 408) and GLPs, this study is considered "2-Reliable with restrictions" and is sufficient to meet this HPV Endpoint requirement.

Dietary levels as high as 2.5% (approximately 1500 mg/kg/d for males and 1950 mg/kg/d for females) produced no systemic toxicity. Measurements included body weights, food

consumption, survival, clinical biochemistry and hematology, organ weights and full necropsies and microscopic examination of a full range of tissues. Of note, no effects on reproductive organs (male or female) were observed in this subchronic study.

Conclusion – A 13-Week study by the oral route of exposure has been conducted with 97 Adipate and is sufficient to evaluate the Repeated Dose toxicity for this chemical. Therefore, no additional data development is needed for this HPV Endpoint. Additionally, the lack of effects seen in the male and female reproductive organs allows this study to be used to support the Reproductive Toxicity Endpoint, as discussed below.

3.0 Mutagenicity and Chromosomal Aberrations

Information on one of the two Mutagenicity Endpoints for HPV assessment is available with 97 Adipate. An Ames mutagenicity test, following OECD Test Guideline 471 and conducted according to GLPs, is summarized in Table 6. This study has been designed as "1-Reliable without restriction", is further described in the Robust Summary section of this Dossier, and is sufficient to meet this HPV Endpoint.

No evidence of mutagenic activity was observed in the Ames test with 97 Adipate. Similarly, 97 Adipate elicited no mutagenic activity when tested in a L5178Y TK +/- Mouse Lymphoma assay in mammalian cells (Solutia Study no. SR-80-532-information not summarized in this Dossier).

Thus, it is concluded that adequate testing has been performed on 97 Adipate to evaluate the Ames Test HPV Endpoint.

Table 6. Summary of Mutagenicity Studies with 97 Adipate and Structurally Related Compounds

	Ames Test Results (TA1535, TA1537, TA98, TA100)	Chromosomal Aberration Test Results
97-Adipate CAS No. 68515-75-3	Neg. with and without S9	No Data
Dioctyl Adipate (DOA) CAS No. 103-23-1 [SURROGATE]	Neg. with and without S9	Neg. – Mouse Micronucleus
Di-n-Hexyl Adipate (DHA) CAS No. 110-33-8 [SURROGATE]	Neg. with and without S9	Neg. – Mouse Micronucleus Neg. – *In vivo* Rat bone marrow cytogenetics Neg – *In vitro* Cytogenetics

No tests for evaluation of Chromosomal Aberration potential of 97 Adipate have been located. However, we have identified studies that would fulfill this HPV Endpoint that have been conducted with two structurally similar adipate esters, DOA and DHA. Studies conducted with DOA were selected as DOA is a C8 branched chain adipic acid ester; DHA is a C6 linear chain adipic acid ester (see structures on page 4). 97 Adipate is itself a mixed, branched and linear C7-C9 chain adipic acid ester. Hence, there is sufficient structural similarity and overlap for these two compounds to serve as Surrogates to evaluate the biological potential of 97 Adipate for this Endpoint.

All Chromosomal Aberration Endpoint studies for these chemicals have been summarized in Table 6 below and are further reported in their own, respective sections of the Robust Summary in this Dossier. Each study is considered "1-Reliable without restriction". In order to provide as complete a comparison of the mutagenic potential of all three chemicals as possible, we also have included in Table 6 the results of Ames tests performed with DOA and DHA, along with 97 Adipate. These Ames Tests also have been summarized and included in the Robust Summary section at the end of this Dossier.

Not only is there a close structural similarity between DOA, DHA and 97 Adipate, there is also a consistent **lack of mutagenic activity** seen with all tests performed with these adipic acid esters. Whether evaluated as to potential to cause Chromosomal aberrations via cell culture or in whole animal testing, DOA and DHA were uniformly without mutagenic activity. Similarly, Ames tests with all 5 tester strains (with and without activation) with each of the three adipate esters were uniformly without mutagenic activity. Thus, we believe it is scientifically valid to conclude that 97 Adipate is highly unlikely to cause chromosomal aberrations and that the results of Chromosomal Aberration test results with DOA and DHA can be used as Surrogates to fulfill this HPV Endpoint rather than to conduct a similar study with 97 Adipate.

In summary, use of surrogate Chromosomal Aberration testing with structurally similar adipate esters is sufficient to meet the HPV Endpoint Testing needs for 97 Adipate. Thus, no further, unnecessary testing is planned.

4.0 Reproductive and Developmental Toxicity

An extensive literature search yielded no studies that directly assessed the reproductive toxicity of 97 Adipate. However, a rat Developmental Toxicity study, which was conducted in accord with GLPs and meets OECD Test Guideline 414, is available. It has been summarized in Table 5, and extensively reported in the Robust Summary section of this Dossier. It is considered "1-Reliable without restriction". Results of this study, coupled with the lack of testicular effects observed in the 13-Week rat Repeated Dose study reported above, is sufficient to meet the HPV criteria for the Reproductive Toxicity Endpoint, as outlined by US EPA (1998).

In summary, when tested via gavage at dosages ranging from 1,000 – 7,000 mg/kg/d and administered between gestation days 6-19, 97 Adipate produced maternal (decreased weight and weight gain) toxicity but no evidence of teratogenic effects. A small increase in skeletal variations was observed at 7,000 mg/kg/d, a level which also produced maternal toxicity.

In conclusion, the Reproductive Toxicity HPV Endpoint has been fulfilled with completion of a rat teratology study coupled with the lack of evidence of test article effects on the reproductive organs (male and female) after subchronic (90-day) testing. Thus, no further testing for this Endpoint is warranted.

V. REFERENCES

EPIWIN, 2002. Version 3.10, Syracuse Research Corporation, Syracuse, New York.

Felder, JD, Adams, WJ, Saeger, VW. 1986. Assessment of the safety of Dioctyl Adipate in freshwater environments. Environmental Toxicology and Chemistry 5: 777-784.

Klimisch, H.-J., Andreae, M. and Tillman, U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

US EPA, 1985. Toxic Substances Control Act Chemical Substance Inventory. TSCA Inventory: 1985 Edition. Volume 1. TS-793. EPA-560/7-85-002a. US Environmental Protection Agency, Office of Toxic Substances, Washington, DC.

US EPA, 1998. Guidance for meeting the SIDS requirements (The SIDS Guide). Guidance for the HPV Challenge Program (11/31/98).

US EPA, 1999a. Determining the adequacy of existing data. Guidance for the HPV Challenge Program (2/10/99).

US EPA, 1999b. The use of structure-activity relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

VI. ROBUST STUDY SUMMARIES

IUCLID Data Sets, full set for 97 Adipate and selected studies for DOA and DHA, are appended